REMARKS

Claims 1-57 are pending in this application, and claims 20-49 are withdrawn from consideration, as directed to non-elected subject matter in response to the November 1, 2005 requirement for restriction.

Independent claims 1, 10, and 19 have been amended to recite that deamidated TFPI or TFPI analog molecules are detected through indirect measurement of isoaspartic acid. New, dependent claims 55-57 further specify this indirect measurement comprises analyzing a byproduct S-adenosyl-homocysteine (SAH) by RP-HPLC, wherein the byproduct is generated from the transfer of a methyl group from S-adenosyl-L-mehionince (SAM) to isoaspartic acid, catalyzed by Protein Isoaspartyl Methyl Transferase (PIMT). Support for these claim amendments and new claims is found in paragraph [49] on page 13 of the specification.

Independent claims 1, 10, and 19 have been amended to delete the word "about" in the phrase "less than about 12% . . . modified species."

The amendments add no new matter.

The Rejections of Claims 1-19 and 50-54 under 35 U.S.C. § 112 (Office Action, pages 2-3)

Claims 1-19 and 50-54 have been rejected as indefinite under 35 U.S.C. § 112, second paragraph. According to the Office Action, "The claim scope is uncertain since the trademark [ISOQUANT®] . . . cannot be used properly to identify any particular material or product." Also, the Office Action deems the phrase "less than about 12%" to be indefinite.

To advance prosecution, the trademarked term ISOQUANT® has been deleted from independent claims 1, 10, and 19. In particular, the phrase "as detected by a Promega ISOQUANT® kit" has been replaced by "as detected through indirect measurement of isoaspartic acid," which characterizes the assay performed by the ISOQUANT® kit without using the trademarked term. See paragraph [49] on page 13 of the specification. New claims 55-57

further characterize this assay in terms of the particular reaction, reagents, and analysis employed.

Additionally, independent claims 1, 10, and 19 have been amended to delete the word "about" in the phrase "less than about 12% . . . modified species," thereby mooting this rejection.

Reconsideration and withdrawal of these rejections under 35 U.S.C. § 112, second paragraph, are respectfully requested.

The Rejections of Claims 1-19 under 35 U.S.C. § 112 (Office Action, pages 3-4)

Claims 1-19 have been rejected as indefinite under 35 U.S.C. § 112, second paragraph, because "the value of 'at least 200 grams' do[es] not have an upper limit and thus the value is open ended and indefinite." Applicants respectfully traverse these rejections insofar as they apply to claims 1-19, as well as new dependent claims 55-57.

Applicants respectfully submit that specifying an upper limit for the amount of TFPI or TFPI analog is not necessary to render the pending claims definite. The breadth of a claim is not to be equated with indefiniteness. *In re Miller*, 441 F.2d 689, 169 USPQ 597 (CCPA 1971). Rather, under the second paragraph of 35 U.S.C. § 112, the relevant inquiry

> . . . is merely to determine whether the claims do, in fact, set out and circumscribe a particular area with a reasonable degree of precision and particularity. It is here where the definiteness of the language employed must be analyzed –not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art.

In re Moore, 439 F.2d 1232, 1235, 58 C.C.P.A. 1042, 1046-47 (1971). The importance of the specification in determining whether the claims are definite also was emphasized in *In re Cohn*, 438 F.2d 989, 993, 58 C.C.P.A. 996, 1001 (C.C.P.A. 1971): "No claim may be read apart from and independent of the supporting disclosure on which it is based."

In this case, one skilled in the art would understand the specification as being directed to the commercial-scale production of TFPI and TFPI analogs. See, for example, paragraphs [29] and [30] on page 8 of the specification. Therefore, claims 1-19 would be understood to cover preparations comprising the recited "at least 200 grams of TFPI or TFPI analog," up to quantities that could be reasonably produced in a commercially practical manner. In view of the specification, pending claims 1-19 and 55-57 "set out and circumscribe a particular area with a reasonable degree of precision and particularity" and are therefore definite.

Reconsideration and withdrawal of these rejections under 35 U.S.C. § 112, second paragraph, are respectfully requested.

The Rejections of Claims 1-19 under 35 U.S.C. § 102

Claims 1-19 and new claims 50-54 are rejected as being anticipated by Diaz-Collier *et al.*, EPO publication EP 0 559 632 A1 ("Diaz-Collier"). Applicants respectfully traverse these rejections insofar as they apply to claims 1-19 and 50-54, as well as new claims 55-57.

In Applicants' prior response filed December 23, 2007, independent claims 1, 10, and 19 were amended to recite a large-scale preparation comprising at least 200 grams of TFPI or TFPI analog. The presently pending claims are therefore focused on the inventive aspect of providing "large-scale preparations of purified TFPI or TFPI analog" (*e.g.*, having at least a 200 gram quantity of the purified protein). See page 8, paragraph [30]. Applicants describe, for example, a commercial scale preparation in which "[t]he amount of TFPI or TFPI analog in the refolding step is 20,000 g." See page 28, paragraph [94].

The ability to manufacture the claimed, highly purified TFPI and TFPI analog preparations on a large scale is a result of Applicants' discovery of a defined sequence of chromatography and other operations, following the refolding of TFPI or TFPI analogs expressed in *E. coli*. These operations are discussed in detail in Applicants' prior response filed

December 23, 2007. Applicants' method was developed as a result of extensive research to provide commercial-scale pharmaceutical compositions comprising TFPI or TFPI analogs which would meet applicable FDA standards for purity in Phase III clinical trials (*e.g.*, less than 12% of modified species, as defined in the pending claims). These purity standards for commercial-scale preparations of TFPI and TFPI analogs were not achieved during attempts to scale up prior art methods.

DIAZ-COLLIER DOES NOT DESCRIBE OR SUGGEST THE CLAIMED, LARGE-SCALE TFPI OR TFPI ANALOG PREPARATIONS

There is no teaching or suggestion in Diaz-Collier that the disclosed method is applicable for producing compositions comprising TFPI or a TFPI analog **in a large-scale quantity of at least 200 grams**, with the claimed level of purity. In fact, in Diaz-Collier's "larger scale" preparation, **only 500 milligrams (mg)** of TFPI protein is purified by cation exchange chromatography (*i.e.*, the final process step following TFPI refolding). See page 11, lines 21-22. This 500 mg scale preparation is consistent with Diaz-Collier's publication of the same method in THROMBOSIS AND HAEMOSTASIS, 71(3): 339-46 (1994). In the final paragraph on page 345 of this publication, the authors remark that "the present *E. coli* system is capable of generating about 300 mg of highly active TFPI from a 10-liter fermentation culture." Nowhere does Diaz-Collier suggest that commercial quantities of at least 200 grams (*i.e.*, about 400-fold greater protein amounts, compared to the disclosed "larger scale" preparation) could be produced.

In response, the Office Action remarks,

> . . . amending the claims to include at least 200 grams of TFPI or TFPI analog does not change the fact that still less than about 12% of the TFPI or TFPI analog molecules are modified. Thus, by increasing the numerical value of TFPI in "grams" does not change the required "percentage" since the percentage is the limiting factor in the claims as presented.
>
> Office Action, pages 5-6.

As discussed above, the invention defined by the currently pending claims is directed to TFPI and TFPI analog preparations having **two important features**, namely (i) commercial-scale quantity (*i.e.*, at least 200 grams) and (ii) commercial-grade purity (*i.e.*, less than 12% modified species). Applicants agree that the feature "at least 200 grams" does not change the percentages of modified species allowed in the claimed preparations. However, this feature does define the total quantity of TFPI or TFPI analogs in these preparations. In fact, this feature alone distinguishes over laboratory-scale preparations, such as those described in Diaz-Collier as being applicable for quantities of several hundred milligrams, as discussed above. Again, the claimed invention, in contrast to Diaz-Collier, is associated with the manufacture of TFPI or TFPI analog preparations having the recited, high level of purity on a commercial scale of at least 200 grams.

"All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382,1385, 165 USPQ 494, 496 (CCPA 1970). The Office Action fails to consider all words in independent claims 1, 10, and 19, and specifically the words "at least 200 grams" in judging their patentability. This claimed feature distinguishes the product; it is not a process limitation, as the Office Action appears to suggest on page 6. Finally, the statement on the same page that ". . . the 500 mg of TFPI taught by EP 0 559 632 is still in the range of 'at least 200 mg' " is completely irrelevant. The claim recites a commercial-scale quantity of at least 200 grams (not milligrams). As stated above and in the response filed

December 23, 2007, the quantity "at least 200 grams" is 400-times greater than the "larger scale" preparation (500 milligrams or 0.5 grams) made according to the method of Diaz-Collier.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Diaz-Collier does not meet the legal standard for anticipation, at least because this reference does not describe or suggest a large-scale, purified preparation or pharmaceutical composition comprising at least 200 grams of TFPI or a TFPI analog, as recited in claims 1-19 and 50-54. New claims 55-57 depend from claim 1 and are therefore patentable for at least the same reasons that claim 1 is patentable.

Reconsideration and withdrawal of the rejections under 35 U.S.C. § 102 are respectfully requested.

The Rejection of Claim 19 under 35 U.S.C. § 103

Claim 19 is rejected as obvious over Diaz-Collier in view of Chen *et al.*, U.S. Patent No. 6,525,102 ("Chen"). Applicants respectfully traverse these rejections.

Claim 19 is directed to a large-scale pharmaceutical composition comprising ala-TFPI. Less than about 12% of the ala-TFPI molecules are modified species, as defined in this claim. The pharmaceutical formulation comprises 20 mM sodium citrate, 300 mM L-arginine, and 5 mM methionine, at pH 5.5. Claim 19 also recites that the pharmaceutical formulation comprises at least 200 grams of ala-TFPI.

A *prima facie* case of obviousness requires that the prior art reference (or references when combined) teach or suggest all the claim limitations. *In re Royka*, 490 F.2d 981, 985, 180 U.S.P.Q. 580, 583 (C.C.P.A. 1974) (emphasis added). For the same reasons given above with

respect to the rejections under 35 U.S.C. § 102, Diaz-Collier neither describes nor suggests a large-scale pharmaceutical formulation comprising at least 200 grams of ala-TFPI as recited in claim 19. Chen fails to cure this deficiency of Diaz-Collier.

In contrast to the disclosures of Diaz-Collier and Chen, Applicants have now found that TFPI or TFPI analog pharmaceutical formulations can be manufactured in commercial-scale (*e.g.*, at least 200 gram) quantities, having the level of purity recited in claim 19.

Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103 are respectfully requested.

CONCLUSION

In view of the above amendments remarks, all pending claims of this application are believed to be in condition for allowance. Acknowledgement of the same is respectfully requested. This response is believed to completely address all of the substantive issues raised in the Office Action dated January 23, 2008.

Please continue to direct all correspondence in this application to Novartis Vaccines and Diagnostics, Inc. (formerly Chiron Corporation), Intellectual Property Dept., R440, 4560 Horton Street, Emeryville, CA 94608-2916.

Respectfully submitted,
BANNER & WITCOFF, LTD.

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